IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Raymond P. WARRELL et al.

Application No.: 09/709,170	Art Unit: 1635
Filed: November 10, 2000	Examiner: Terra C. Gibbs
For: METHODS OF TREAMENT OF A BCL-2 DISORDER USING BCL-2 ANTISENSE OLIGOMERS	Confirmation No.: 4982
	Atty. Docket No.: GEN0008-01US

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

REPLY BRIEF

Sir:

This paper is submitted in response to the Examiner's Answer mailed on December 11, 2008, in the above-identified application. Submission of a reply brief in this case is due by February 11, 2008. Accordingly, this paper is being timely filed. Appellants respectfully request that the following remarks be considered.

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1. Status of the Claims

Claims 1, 3-5 and 7-23 were finally rejected in an Office Action mailed on March 25, 2008 ("the Final Office Action"), and are the subject of this appeal. Claims 2, 6 and 24-33 were previously cancelled without prejudice or disclaimer.

2. Related Appeals and Interferences

Appellants would like to point out that subsequent to the submission of the Appeal Brief in the instant application, Applicants filed a Notice of Appeal and Appeal brief in U.S. Patent Application No. 10/738,867, which claims priority from the instant application.

3. Grounds of Rejection to be Reviewed on Appeal

Whether claims 1, 3-5 and 7-23 are unpatentable under 35 U.S.C. § 103(a) as obvious over Webb et al. (*Lancet* 349:1137-1141 (1997); "Webb") in view of Waters et al. (*J. Clin. Oncol.* 18:1812-1823 (2000); "Waters") and Bennett et al. (U.S. Pat. No. 6,214,986; "Bennett").

4. Argument

Appellants respectfully set forth this Reply Brief on the ground that, like the Final Office Action, the Examiner's Answer fails to provide a rational basis on which to rely to justify a modification to the prior art references to arrive at the appealed claims. No expectation of success has been set forth either. *Prima facie* obviousness, therefore, has not been established, and the rejection of the pending claims should be reversed.

In the Examiner's Answer, the basis and main focus of the rejection continues to be the fact that Webb taught a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide in a cycle of therapy comprising 14-days. Waters allegedly provided motivation to administer the antisense oligonucleotide in more than one cycle of therapy, and Bennett allegedly provided motivation to shorten the 14-day course of therapy taught in the prior art. One skilled in the art, according to the Examiner, using nothing more than routine experimentation and testing, would be motivated to shorten the 14-day course of therapy taught in the art. Appellants continue to disagree with the Examiner's approach, although Appellants do agree with the Examiner's decision to not rely on inherency as a basis for the § 103 rejection.

Appellants maintain that the mere boilerplate language in Bennett simply ***cannot*** be substituted for the perspective that one skilled in the art provides as to the meaning and import of the Webb reference. That is, the Examiner's continued disregard of the analysis and conclusions provided in Dr. Novick's declaration and her continued reliance on mere boilerplate language are entirely improper.

As explained in Appellants' Appeal Brief, Webb and Waters are limited to a 14-day treatment course, while Bennett merely discloses boilerplate language concerning

possible dosing regimens for ASOs. The passage relied upon by the Examiner in Bennett reads in full:

> The formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50}s found to be effective in in vitro and in vivo animal models. ***In general, dosage is from 0.01 µg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years.*** Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the oligonucleotide is administered in maintenance doses, ranging from 0.01 µg to 100 g per kg of body weight, once or more daily, to once every 20 years.

As highlighted, Bennett teaches that the ASO may be given for a period ranging from ***once a day to once every 20 years***. It is hard to imagine a broader range of administration. No other guidance is given. Clearly, such a disclosure adds nothing over the teachings of Webb and Waters.

Dr. Novick makes clear in his declaration that one skilled in the art would not have shortened the 14-day cycle in Webb, regardless of reduced bcl-2 levels in Webb or Bennett's boilerplate language regarding optimal dosing of ASOs. Notwithstanding the disagreement with the Examiner as to the impressiveness of the results in Webb, Dr.

Novick, as one skilled in the art, concludes in his declaration that the mere fact that one patient (patient 6) had reduced levels of bcl-2 would not have provided any motivation to shorten the course of treatment. *See id.*, page 3, ¶ 12. As indicated by Dr. Novick, one would understand that bcl-2 levels would in all likelihood decrease with bcl-2 ASO treatment, but would not know whether this reduction was transient or stable. *See id.*, page 3, ¶ 13. Furthermore, one would not know whether such a reduction had any efficacy against cancer, particularly if transient. *See id.* As such, rather than reducing the course of therapy, one skilled in the art would be motivated to continue with the longer course of therapy, perhaps with a higher dose of bcl-2 ASO, or add to the regimen a second, third or fourth (or more) course of therapy, or some combination thereof. *See id.*, page 3, ¶ 14. As such, the Examiner has failed to establish any rational basis for modifying the cited art.

Moreover, the Examiner has provided no evidence to refute Dr. Novick's conclusions. The Examiner merely states that she disagrees that the results of Webb were "overall unsatisfactory," based upon the improvement in symptoms and tumor shrinkage in patients 6 and 8. However, as indicated in Dr. Novick's declaration, one of skill in the art would not know whether the total infusion of 14 days (the time of treatment for both patients 6 and 8) was necessary to provide treatment of cancer, or whether infusion for a shorter period of time would be sufficient, particularly since the other treated patients showed no tumor response. *See id.*, page 3, ¶ 12. In this light, Appellants submit that the Examiner has merely substituted her opinion regarding efficacy for that of the skilled artisan's, which constitutes reversible error. *See In re Ridyard*, Appeal No. 1996-0740, 2001 Pat. App. LEXIS 132, at (BPAI 2001) ("[I]n stating that '[i]n this case the

differences are not truly surprising and unexpected' . . ., the examiner has improperly substituted his opinion for the opinion of an expert in the art.") (citing *In re Zeidler*, 682 F.2d 961, 966-67 (CCPA 1982) ("[B]ecause the qualifications of Lach and the test procedures which he employed are unchallenged, the board's holding that 'a more dramatic difference in result' is required constitutes reversible error, the board having erroneously substituted its judgment for that of an established expert in the art.")).

Furthermore, none of the evidence relied upon by the Examiner provides any expectation of success for the specifically claimed cancer treatment. No showing has been made that reducing the time of administration below 14 days (in particular the claimed 3-9 days) would be efficacious in the treatment of cancer. The disclosures identified by the Examiner are merely invitations to experiment in an unpredictable field, with no reasonable expectation of success identified in the art. *See Pfizer, Inc. v. Apotex, Inc.*, 488 F.3d 1377, 1384 (Fed. Cir. 2007) ("Furthermore 'obvious to try' jurisprudence has a very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis."); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[P]rior art fails to provide the requisite 'reasonable expectation' of success where it teaches merely to pursue a general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.") (internal quotation marks omitted); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art

teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure.").

The Examiner, citing *In re Peterson*, states in the Examiner's Answer that the optimization of the 14-day course of treatment would flow from the "normal desire of scientists or artisans to improve upon what is already generally known." However, this quotation is taken out of context. In *Peterson*, the claimed ranges for each of the components were completely ***encompassed*** within the prior art. The court stated that "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where ***in a disclosed set of percentage ranges is the optimum combination of percentages***." 315 F.3d at 1330 (emphasis added). Here, the claimed cycle of therapy (3-9 days) is not encompassed within, nor does it overlap, the treatment schedules identified in the prior art, all of which are 14 days or more. Rather, it is a distinct treatment over a ***substantially shorter*** period of time than that disclosed in the prior art. As explained above, and confirmed by Dr. Novick, nothing in Webb and Waters, even in view of Bennett, would have led one of ordinary skill in the art to shorten the standard bcl-2 ASO treatment schedule of 14 days at all, let alone to the claimed period of 3-9 days, or that doing so would have had a reasonable expectation of success.

Appellants maintain that the Examiner's rejection rests on nothing more than the assertion that it is always obvious to modify a therapeutic dosing regimen to achieve optimal results, even in the face of teachings to the contrary. However, as indicated in Appellants' Appeal brief, "obvious to try" is not the standard in this case:

> The PTO and the minority appear to argue that it would always be obvious for one of ordinary skill in the art to try

> varying every parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result. As we have said many times, obvious to try is not the standard of 35 USC 103. *In re Tomlinson*, 53 CCPA 1421, 363 F.2d 928, 150 USPQ 623 (1966). Disregard for the unobviousness of the results of "obvious to try" experiments disregards the "invention as a whole" concept of § 103, *In re Dien*, 54 CCPA 1027, 371 F.2d 886, 152 USPQ 550 (1967) and *In re Wiggins*, 55 CCPA 1356, 397 F.2d 356, 158 USPQ 199 (1968), and overemphasis on the routine nature of the data gathering required to arrive at appellant's discovery, after its existence became expected, overlooks the last sentence of § 103. *In re Saether*, 492 F.2d 849, 181 USPQ 36 (CCPA 1974).

In re Antonie, 559 F.2d 618, 620 (CCPA 1977).

As in *Antonie*, the Examiner has overemphasized the so-called "routine" nature of the clinical data gathering necessary to establish and support the claimed method of treatment, particularly after its acceptance by others in the art, and has failed to give proper weight to the nonobviousness of the invention "as a whole" under § 103. When viewed under the proper test, Appellants maintain that the Examiner has failed to make out a *prima facie* case of obviousness of claims 1, 3-5 and 7-23.

CONCLUSION

For the foregoing reasons, Appellants maintain that claims 1, 3-5 and 7-23 are not unpatentable over Webb in view of Waters and Bennett, and reversal of the Examiner's rejections is therefore appropriate and respectfully solicited.

Respectfully submitted,

Date: February 9, 2009

By: /Karen Millane Whitney, Reg. No. 52,355/
Karen Millane Whitney
Reg. No. 52,355

Diehl Servilla LLC
77 Brant Avenue, Suite 210
Clark, New Jersey 07066
TEL (732) 815-0404
FAX (732) 815-1330
Attorneys for Appellants